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REVIEW ARTICLE

Orbital and optic nerve complications of inflammatory bowel disease



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Received 2 July 2012; received in revised form 11 September 2012; accepted 27 September 2012

KEYWORDS

Inflammatory bowel disease;
Optic neuritis;
Retrobular neuritis;
Orbital pseudotumor;
Orbital inflammatory disease;
Anti-TNF

Abstract

Background and aims: Extraintestinal manifestations of inflammatory bowel disease (IBD) can involve the orbit and the optic nerve. Although these manifestations are rare, they can be particularly serious as they can lead to permanent loss of vision. The aim of the review is to present the existing literature on IBD-related optic nerve and orbital complications.

Methods: A literature search identified the publications reporting on incidence, clinical features and management of IBD patients with optic nerve and orbital manifestations.

Results: Posterior scleritis and orbital inflammatory disease (orbital pseudotumor) are the most commonly encountered entities affecting the structures of the orbit. On the other hand, the optic nerve of IBD patients can be affected by conditions such as optic (demyelinating) neuritis ("retrobular" neuritis), or ischaemic optic neuropathy. Other neuro-ophthalmic manifestations that can be encountered in patients with IBD are related to increased intracranial pressure or toxicity secondary to anti tumour necrosis factor (anti-TNF) agents.

Conclusions: IBD-related optic nerve and orbital complications are rare but potentially vision-threatening. Heightened awareness and close cooperation between gastroenterologists and ophthalmologists are warranted.

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Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; IH, intracranial hypertension; OID, orbital inflammatory disease; TNF, tumour necrosis factor; UC, ulcerative colitis.

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<http://dx.doi.org/10.1016/j.crohns.2012.09.020>

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1. Introduction

The prevalence of ophthalmic manifestations in patients with IBD remains a matter of controversy. Although earlier surveys and chart review studies have estimated the prevalence of ocular findings in IBD at 3.6–6.3%,^{1–5} a population-based study has found ocular involvement in 1%–2% of IBD patients.⁶ On the other hand, tertiary centre surveys indicate that ocular findings in IBD patients may be significantly more prevalent when a thorough evaluation by an ophthalmologist is performed.⁷ In

fact, in their survey, Yilmaz et al.⁸ found that 60% of their CD patients had ocular findings.

This review presents the rare but potentially blinding extraintestinal manifestations of IBD that involve the optic nerve and the other elements located in the orbit, i.e. extraocular muscles, lacrimal gland and posterior sclera (Figs. 1 and 2). The rationale of including these particular extraintestinal manifestations in the current article is related both to the anatomical proximity of the involved elements, and the frequently overlapping and confusing clinical signs and symptoms produced by orbital conditions.

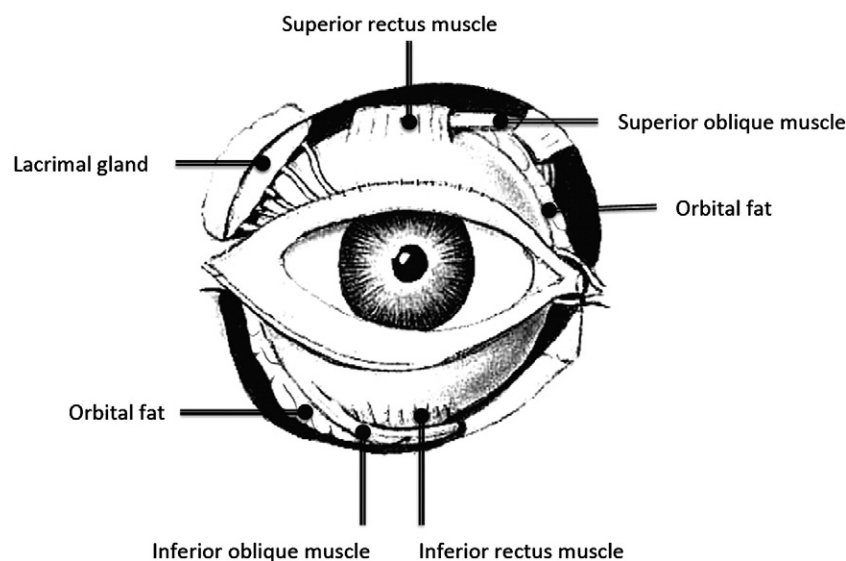


Figure 1 Schematic diagram of the anterior aspect of the right orbit.

2. Orbital complications in patients with inflammatory bowel disease

2.1. Clinical spectrum

2.1.1. Orbital pseudotumor

One of the least frequent, yet potentially sight-threatening ophthalmic manifestations of IBD is "orbital pseudotumor". This non-specific term is loosely used to describe the enlargement of retrobulbar anatomical elements due to inflammation. The resultant symptoms and signs often resemble those of retrobulbar tumours. Other terms often used to describe this clinical entity include "orbitopathy", and "orbital inflammatory disease" (OID). The condition can be idiopathic, or occur in association with a number of systemic inflammatory diseases.^{9–12}

Orbital pseudotumor is a rare extraintestinal manifestation of IBD and virtually all available evidence comes from sporadic case reports. Consequently, its exact association with clinical characteristics of the intestinal disease and patient demographics is uncertain. Lakatos et al.,¹³ in a 25-year follow-up study of 873 patients with IBD found only one case of orbital pseudotumor in a woman with severe ulcerative pancolitis. Nonetheless, published case reports indicate that the condition is most commonly associated with CD, rather than UC and the majority of patients are women (Table 1). Although the pathogenesis of orbital inflammatory disease in patients with IBD is unknown, it is generally thought that immune-mediated processes are involved. For example, an immune-complex-type hypersensitivity reaction to a colonic antigen has been suggested. This view is supported by the observation that IBD patients with colitis or ileocolitis are more likely to have ocular inflammation than those with only small bowel disease.^{14,15}

In contrast to ocular manifestations of IBD such as uveitis,² the existing literature suggests that orbital complications are not associated with a distinct pattern of intestinal disease activity, duration or phenotype.

The clinical manifestations may vary widely depending on the structures affected by the combined effects of inflammation, orbital pressure elevation and direct compression. Retro-orbital pain (often worse at night and/or with eye

movements), diplopia, ophthalmoplegia, proptosis, eyelid swelling, decreased vision, conjunctival chemosis and injection are all common findings.

2.1.2. Orbital myositis

Orbital myositis is a common subtype of orbital pseudotumor in which one or more of the extraocular muscles are affected. The clinical presentation is typically characterized by acute onset, severe pain inside, behind or around the eye, pain on eye movement, occasional diplopia and conjunctival chemosis. A prompt response to a therapeutic trial of systemic steroids is typical, but recurrences are common.

2.1.3. Posterior scleritis

With the exception of exophthalmos, the remaining symptoms and signs accompanying orbital myositis are often encountered in IBD patients with posterior scleritis. This condition is a potentially serious, usually painful disease of the sclera, which can seriously affect vision if not managed appropriately. Depending on whether the anterior or the posterior segment of the eye is affected, scleritis can respectively be characterized as anterior or posterior. Although most types of anterior scleritis do not normally result in major complications if treated early, posterior scleritis frequently results in visual loss. The worse prognosis and more frequent complication occurrence in cases with posterior scleritis is explained by the fact that the posterior sclera is impossible to visualize and can only be assessed by means of ultrasonography or indirectly through the effects that scleritis can cause to the overlying choroid and retina (e.g. choroidal folds, exudative retinal detachment, etc.). Importantly, macular involvement due to the neighbouring inflammation can seriously affect central vision.

2.1.4. Dacryoadenitis

An exceptionally rare orbital manifestation in patients with CD is inflammatory involvement of the lacrimal gland (dacryoadenitis). Typical signs and symptoms include tender swelling of the upper eyelids with discomfort and lacrimation.^{16–18}

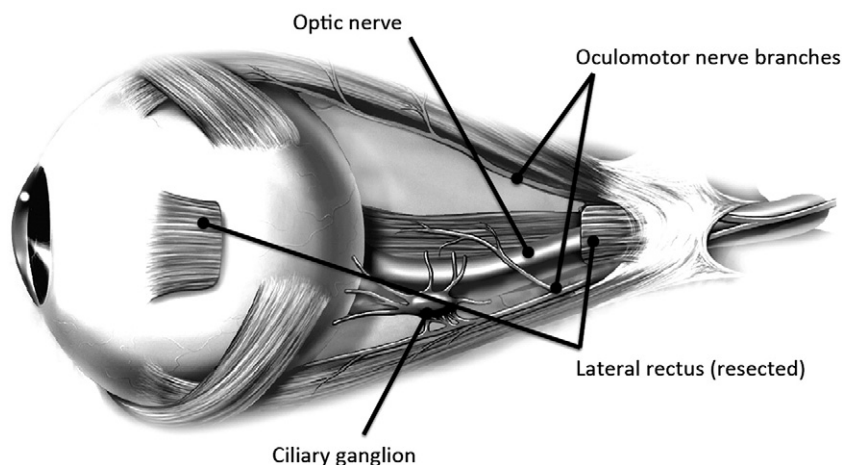


Figure 2 Schematic diagram of the temporal aspect of the left orbit.

Table 1 Reported cases of orbital involvement in patients with inflammatory bowel disease (IBD) along with their clinical characteristics and treatment. (M: man, W: woman, CD: Crohn's disease, UC: ulcerative colitis).

Age/sex	Presentation	IBD	Preceding vs following IBD diagnosis	Treatment	Comment	Reference
38/W	Unilateral painful eye, diplopia	UC	Following (12 years)	Systemic steroids	Similar episode in contralateral eye	Jain and Gottlob ²¹
32/M	Unilateral proptosis	UC	Following (3 years)	Systemic steroids		Macarez et al. ⁸¹
"Young"/W	Unknown	UC	Unknown	Unknown	Severe pancolitis	Lakatos et al. ¹³
12/W	Bilateral periorbital oedema, ptosis, proptosis	CD	Preceding (8 months)	Prednisone 2 mg/kg/day	Bilateral recurrences	Durno et al. ⁸²
14/W	Bilateral proptosis, conjunctival injection, unilateral eye pain, headache, diplopia	CD	Preceding (approximately 8 months)	Prednisone 60 mg/day, bowel resection	Bilateral recurrences	Young et al. ⁸³
15/W	Bilateral proptosis, eye movement restriction, eyelid oedema, photophobia, bitemporal headache, eye pain on movement, conjunctival injection	CD	Preceding (1 month)	Dexamethasone 16 mg/day Prednisone 40 mg/day		Camfield et al. ⁸⁴
17/W	Unilateral orbital pain, upper eyelid oedema, diplopia, ptosis.	CD	Preceding (Crohn's disease diagnosed during work-up for orbital condition)	Prednisone 60 mg/day		Weinstein et al. ⁸⁵
40/W	Bilateral eye pain with movement, diplopia, blurry vision and periorbital oedema in right eye	CD	Following (approximately 20 years)	Prednisone 60 mg/day	Possibly numerous previous attacks	Ramalho and Castillo ¹⁴
38/W	Bilateral eye pain with movement, diplopia. Left eye: visual field loss and visual acuity reduction	CD	Following (6 years)	Pulse methylprednisolone and oral steroids	Left eye: optic nerve compressed due to extraocular muscle enlargement	Cheng et al. ⁸⁶
23/W	Unilateral periorbital pain, frontal headache, diplopia, conjunctival injection, chemosis	CD	Following (8 years)	Pulsed methylprednisolone (1 g/day for three days), i.v. cyclophosphamide (15 mg/kg every two weeks, six doses), oral prednisolone 15 mg/day for twelve weeks	Previous bilateral attacks of posterior scleritis	Culver et al. ⁸⁷

32/W	Bilateral ocular pain, periorbital swelling, ptosis, diplopia	CD	Preceding (2 years)	Corticosteroids 1 mg/kg daily (sic), cyclosporine (sic), adalimumab 40 mg every other week	Orbital inflammation uncontrolled with combination of steroids and cyclosporine	Hernández-Garfella et al. ²⁸
35/W	Unilateral proptosis	CD	Preceding (1 year)	Steroids (sic)	Diagnosis of orbital inflammation was based on past MRI	Bourikas et al. ⁸⁸
20/M	Unilateral eye pain with movement, frontal headache, diplopia,	CD	Following (8 years)	Prednisone 60 mg/day	Contralateral attack of orbital inflammation during tapering	Squires et al. ⁸⁹
44/M	Unilateral periorbital pain and oedema, proptosis, restriction of gaze	CD	Following (several years)	Prednisolone 100 mg/day	Suppurative granulomatous myositis	Leibovitch et al. ⁹⁰
38/W	Frontal headache, eyelid swelling, conjunctival hyperaemia, diplopia, exophthalmos	CD	Following	Prednisolone 20 mg b.i.d.		Verbraeken et al. ⁹¹
54/W	Unilateral proptosis and discomfort, diplopia	CD	Following (21 years)	Prednisone 60 mg/day	Contralateral recurrence one year later	Smith ⁹²
48/W	Unilateral proptosis, periorbital pain and oedema, diplopia, chemosis,	CD	Preceding (2 years)	Prednisone 60 mg/day	Uni- and contralateral recurrences	Maalouf et al. ¹⁸
34/W	Unilateral periorbital swelling, proptosis, and painful diplopia	CD	Unknown	Poor results with prednisone and methotrexate. Acceptable control with infliximab and methotrexate 15 mg/week		Garrity et al. ²⁵
27/W	Unilateral myositis	CD	Preceding (2 years)	Poor results with per os and retrobulbar steroids, methotrexate and radiotherapy. Good control with infliximab only		Garrity et al. ²⁵
55/W	Unilateral periorbital pain and oedema, diplopia, ptosis, exophthalmos.	CD	Following	Prednisolone 125 mg/day. Later infliximab (maintenance with 5 mg/kg every 8 weeks)	Contralateral recurrence	Pimentel et al. ⁹³

2.2. Investigations and diagnosis

The diagnostic work-up should aim primarily at differentiating OID from infectious orbital cellulitis and thyroid orbitopathy. Orbital cellulitis is a potentially life-threatening condition frequently associated with trauma, antecedent sinus disease or dental procedures, and is often accompanied by the classic signs of periocular erythema, oedema, localized warmth and tenderness. Fever and leukocytosis are also typical, but all these features are uncommon in noninfectious OID. Patients with infectious orbital cellulitis are usually hospitalized and treated with high doses of i.v. antibiotics in order to avert potentially serious complications such as cavernous sinus thrombosis or intracranial extension of the septic inflammation with resultant brain abscess or meningitis.

Thyroid orbitopathy poses the most frequent differential diagnostic challenge. Typically, this condition has a painless and insidious onset, is often symmetrical, slowly progressive, and sometimes accompanied by systemic manifestations of Graves' disease. Upper eyelid retraction, reduction of the blinking frequency and limitation of movement opposite to the affected muscle are additional findings pointing towards thyroid orbitopathy.

Magnetic resonance imaging (MRI) can be invaluable in the assessment of orbital conditions. In thyroid orbitopathy, tendinous insertions are typically unaffected and the inflammatory swelling of extraocular muscles is usually limited to muscle bellies, which remain well defined. In orbital myopathy, on the other hand, involvement of the tendons is usual and the affected muscles tend to have irregular or blurred contours.^{14,19,20} Another difference often observed is that thyroid orbitopathy affects multiple muscles, whereas orbital myositis induces inflammation to a single muscle.²¹ The most commonly affected muscles are the superior recti and oblique muscles, as well as the medial recti. In general, inflammatory infiltrates exhibit low signal intensity on T1-weighted images, variable intensity on T2-weighted images, and marked, diffuse, and irregular gadolinium enhancement. The long-standing, sclerosing variant of orbital inflammatory disease, on the other hand, usually shows decreased signal intensity on T2-weighted images.¹⁴

Despite the fact that MRI is the most commonly used modality for the assessment of orbital conditions, there may still exist a role for orbital ultrasonography in selected cases.¹⁹ Orbital ultrasonography is a fast and inexpensive modality for the evaluation of extraocular muscle insertions, the examination of the posterior aspect of the globe for signs of scleritis, and the examination for the presence of orbital vascular malformations and intra- or extraocular tumours. Orbital tissue biopsy is rarely indicated unless the clinical picture is uncharacteristic or the response to treatment is minimal. In cases of suspected dacryoadenitis, fine needle biopsy is very rarely indicated, since a prompt response to a therapeutic trial with steroids, together with ultrasound and MRI imaging can nearly always differentiate dacryoadenitis from lacrimal gland teratomas and neoplasms.

Other, much less frequent entities that need to be considered in the differential diagnosis include tumour with or without acute inflammation, lymphoma, carotid-cavernous fistula, and infiltrative myopathies.^{16,20,22–24}

2.3. Treatment

The management of patients with OID mainly consists of steroid administration per os or intravenously. The typical scheme involves prednisone at a dose of 1 mg/kg/day. In most patients, the response is favourable with rapid control of symptoms. The anti-TNF α agent infliximab has been shown to be useful in case reports and short series of patients with recalcitrant or relapsing orbital inflammation and various systemic inflammatory diseases including Crohn's disease.^{25–27} Hernández-Garfella et al.²⁸ also reported favourable results with adalimumab in a patient with Crohn's disease and recurrent orbital myositis. The role of radiotherapy remains a matter of debate, as chart review studies have reported both favourable and less favourable results in patients with difficult-to-control idiopathic orbital inflammation.^{29–32} Rarely, long-standing refractory cases may need to be managed surgically with orbital decompression. Because orbital inflammatory disease can pose a significant danger to the optic nerve if severe and/or long-standing, visual acuity and visual field testing should not be neglected during follow-up.

3. Optic nerve complications in patients with inflammatory bowel disease

Optic nerve involvement in patients with IBD can occur as a result of any of the following causes:

- Damage of the optic nerve tissue per se as a result of inflammation and/or ischaemia
- Intracranial hypertension
- Secondary to anti-tumour necrosis factor (anti-TNF) agents.

3.1. Clinical spectrum

3.1.1. Damage due to inflammatory and/or ischaemic insults

In the case of direct optic nerve involvement, the clinical manifestations may be those of neuroretinitis,³³ papillitis,^{34–37} optic (demyelinating) neuritis (also referred to as "retrobulbar" neuritis),³³ or ischaemic optic neuropathy.^{38,39} The pathomechanism responsible for neuroretinitis, papillitis and retrobulbar neuritis is related to direct involvement of neural tissue by peripapillary or retrobulbar inflammation.⁴⁰ On the other hand, the pathomechanism of ischaemic optic neuropathy is related to occlusion of the vascular bed supplying the optic nerve secondary to inflammation⁴¹ or hypercoagulability.^{41–44}

The association of IBD and demyelinating conditions such as multiple sclerosis (MS), optic neuritis, myelitis, or Guillain-Barre has been suggested. Retrospective cohort and chart review studies have suggested that the concurrence of IBD and demyelinating diseases is more frequent than expected.^{45–47} As discussed later, the use of the recently-introduced anti-TNF α agents might further increase the risk of demyelinating events in patients with IBD.

The limited existing literature does not suggest any distinct pattern of association between intestinal disease activity,

duration or phenotype and optic nerve extraintestinal complications.

3.1.1.1. Neuroretinitis and papillitis. In both neuroretinitis and papillitis, painless blurring of vision and variable decline of visual acuity are usual symptoms. Relative afferent pupillary defects and colour perception abnormalities are also frequent. In patients with neuroretinitis, fundoscopy reveals inflammation of the optic nerve head with involvement of the retina. Typical findings include optic disc swelling with hyperaemia, retinal oedema with cotton-wool spots, vascular engorgement at the involved segments, and vitreous haziness. Fundus fluorescent angiography is useful as a confirmatory test. Papillitis is associated with swelling of the optic nerve head with signs of neuroretinal tissue inflammation, vascular engorgement and optic disc or peripapillary haemorrhages.

3.1.1.2. Optic (demyelinating) neuritis. Optic neuritis can also present with similar complaints of blurry and/or decreased vision over a period of few hours to several days, but is often accompanied by retrobulbar pain, sometimes worsening with eye movements and at nighttime. In contrast to neuroretinitis and papillitis, fundoscopic findings in retrobulbar neuritis are typically absent. However, if previous attacks have occurred, optic disc pallor can be seen (Fig. 3).

3.1.1.3. Ischaemic optic neuropathy. This entity usually presents with sudden painless visual acuity decline, frequently accompanied by an altitudinal visual field defect. Depending on whether the vascular insult occurred at the vicinity or relatively far from the optic disc, fundoscopic findings may vary. In the vast majority of cases, the vascular supply of the anterior portion of the optic nerve is affected and fundoscopy reveals optic disc swelling with tiny splinter haemorrhages and indistinct optic disc margins (Fig. 4). The altitudinal visual field defects of patients with ischaemic



Figure 3 Fundus photograph of a patient's right eye showing optic disc pallor and atrophy as a result of repeated episodes of optic neuritis.



Figure 4 Fundus photograph from the right eye of a patient with non-arteritic anterior ischaemic optic neuropathy. The margins of the disc are indistinct, the neuroretinal tissue is elevated and whitish due to oedema. Splinter-like peripapillary haemorrhages are also seen.

optic neuropathy point towards a vascular insult in the distribution of the posterior ciliary arteries affecting mainly the anterior (prelaminar) portion of the optic nerve.^{38,48}

It should be noted that neuro-ophthalmic manifestations in IBD patients might sometimes present bilaterally. For example, Heuer et al.³⁸ described the case of a 24-year old man with Crohn's disease and bilateral ischaemic optic neuropathy, whereas Lee et al.³⁷ described the case of a 37-year old woman with Crohn's disease and bilateral retrobulbar neuritis. Also, Barabino et al.⁴⁹ described a case of bilateral presumed demyelinating optic neuritis in an 11-year old boy with CD.

Recurrences of retrobulbar neuritis are not uncommon. Often, however, the unequivocal documentation of previous optic neuropathy attacks is lacking, but the patients may report episodes of blurred vision sometimes accompanied by retrobulbar pain. Such typical history, when accompanied by optic disc pallor or frank atrophy and compatible visual field defects, is strongly supportive of recurrent optic neuropathy attacks. Alternate optic neuritis in the right and left eye has also been described in a 50-year old man with UC over the course of few years.⁵⁰ Retrobulbar neuritis in IBD patients can occur without signs of ocular inflammation such as uveitis or retinitis. For example, in a short case series, Sedwick et al.³³ found that three of five IBD patients with clinical findings consistent with retrobulbar neuritis had no evidence of ocular inflammation at presentation. Moreover, van de Scheur et al.⁵¹ described a patient with Crohn's disease and bilateral retrobulbar neuritis without other evidence of ocular inflammation.

3.1.2. Damage due to intracranial hypertension

Intracranial hypertension (IH) can also be the cause of optic nerve involvement in patients with IBD. In addition to the typical symptoms of headache, nausea, vomiting, tinnitus,

and neck or back pain, frequent ophthalmic complains may include blurred or dimmed vision, visual field scotomas, and short episodes of vision loss or flashing lights (photopsiae). Of interest to gastroenterologists is the fact that steroid treatment has been implicated in some case reports as a factor that may cause idiopathic IH.^{52–54} Although the precise mechanism of such an adverse effect is poorly understood, it has been suggested that IH may not be directly linked to steroid use per se, but may instead occur due to cerebral vein and cerebral sinus thrombosis in patients with defective coagulation mechanisms and hyperviscosity.^{55,56} Indeed, short series and a cohort study showed that patients with IBD have several abnormalities in their blood clotting system that may predispose to vascular incidents.^{41–43,57} Corticosteroid withdrawal has also been associated with IH in case reports of few patients with UC and CD through an unknown mechanism.^{58,59} Idiopathic IH has also been described in three patients treated with mesalamine,⁶⁰ sulfasalazine⁶¹ or mesalazine.⁶² Headache is not an infrequent adverse effect of these medications. Since headache is also a very common symptom in patients with IH, the clinical implication is that patients receiving the afore-mentioned medications and complain of headache should be evaluated by an ophthalmologist so that the possibility of idiopathic IH is excluded.

3.1.3. Damage resulting from anti-TNF α adverse events

Several cases of optic neuropathy have been linked to anti-TNF α agents in patients treated for various inflammatory diseases. Infliximab, and more recently adalimumab, have been successfully used for the management of patients with IBD. Infliximab in particular has been incriminated for retrobulbar optic neuropathy in patients with rheumatoid arthritis,^{63–67} UC^{68,69} and CD^{70–73} (Table 2). In general, signs of optic neuropathy appear several months after the initiation of anti-TNF α treatment.⁶⁵ Typical symptoms and signs include retrobulbar pain worsened by ocular movement, visual acuity reduction, relative afferent pupillary defect, colour perception abnormalities, and visual field defects with central or ceco-central scotomas. Fundoscopy is often normal, but MRI reveals optic nerve demyelination. The concurrent presence of demyelinating lesions in the central nervous system has been described and can raise the

possibility of multiple sclerosis: Bidagouren et al.⁶⁶ have reported the case of a 76 year old woman treated with infliximab for rheumatoid arthritis who presented with retrobulbar neuritis and demyelination brain plaques.

The clinical importance of isolated retrobulbar optic neuropathy in patients treated with anti-TNF α agents is related to the fact that some of these patients may eventually manifest multiple sclerosis.⁷⁴ It remains unknown, however, if anti-TNF α -induced optic nerve demyelination carries the same prognostic relevance with regard to future manifestation of MS, or it merely represents an isolated event. In other words, it remains to be determined if anti-TNF α agents can de novo lead to demyelinating diseases such as MS or retrobulbar neuritis, or if they merely unmask a patient's existing predisposition for such diseases. In any event, it seems prudent to consult and closely monitor anti-TNF α -treated patients for the occurrence of ophthalmic or neurological symptoms and signs. In such an event, discontinuation of the anti-TNF α agent and commencement of steroid treatment are mandatory.

Besides demyelinating retrobulbar neuritis, rare cases of toxic anterior optic neuropathy have also been described in infliximab-treated patients. ten Tusscher et al.⁷⁵ were the first to describe three cases of bilateral anterior toxic neuropathy in middle-aged patients with rheumatoid arthritis following their third infliximab infusion. Chan and Castellanos⁷⁶ also described a case of bilateral toxic anterior optic neuropathy in a 68-year old man with Crohn's oesophagitis who developed acute symptoms during his third infliximab infusion. In all reports, the patients' clinical picture was characterized by bilaterally decreased vision with mostly central or inferior visual field defects. Fundoscopy revealed swollen optic discs with capillary dilation and leakage at fluorescent angiography. In contrast to cases with retrobulbar neuropathy, MRI of the optic nerves was normal, since demyelination was not the pathomechanism behind these attacks. To exclude the possibility of optic neuropathy secondary to giant cell arteritis, corticosteroids were administered in all cases but the response was invariably poor and recovery was not observed. The peculiar occurrence of all incidents during, or shortly after the third infliximab infusion might suggest that the toxicity of this medication is dose- or time-dependent.

Adalimumab has also been associated with demyelinating optic neuropathy in patients with various inflammatory conditions. So far, however, no such events have been published in adalimumab-treated patients with IBD. Chung et al.⁷⁷ were the first to describe two cases of unilateral retrobulbar neuritis in a 40-year old man with rheumatoid arthritis and a 55-year old man with psoriatic arthritis. Of note, Li et al.⁷⁸ and Kim and Saffra⁷⁹ have reported cases of patients with recalcitrant ophthalmic inflammation who were treated with adalimumab and developed both retrobulbar neuritis and multiple sclerosis. Similarly, Bensouda-Grimaldi et al.⁷⁴ described the case of a 32-year old woman with rheumatoid arthritis who had been treated with adalimumab for two years and developed retrobulbar optic neuritis as a first manifestation of MS.

3.2. Investigations and diagnosis

In general, the diagnoses of neuroretinitis, papillitis, optic neuritis and ischaemic optic neuropathy are based on the

Table 2 Neuro-ophthalmic manifestations in infliximab-treated patients with Crohn's disease (CD) or ulcerative colitis (UC) (M: man, W: woman).

Age/sex	Inflammatory bowel disease	Neuro-ophthalmic manifestation	Reference
44/M	UC	Optic neuritis	Hejazi et al. ⁶⁸
51/W	UC	Optic neuritis	Mumoli et al. ⁶⁹
50/W	CD	Optic neuritis	Mejico ⁷⁰
54/W	CD	Optic neuritis	Strong et al. ⁷¹
32/M	CD	Optic neuritis	Felekis et al. ⁷²
55/M	CD	Optic neuritis	Ouakaa-Kchaou et al. ⁷³
68/M	CD	Bilateral toxic anterior optic neuropathy	Chan and Castellanos ⁷⁶

characteristic ophthalmic findings already mentioned. Visual acuity, visual field testing, fundoscopy and fundus fluorescent angiography are necessary both for the diagnosis and follow-up. It is important, however, to ensure that no other underlying systemic or ophthalmic infectious or autoimmune condition is responsible for the patient's condition. In cases of suspected retrobulbar optic neuritis, MRI of the orbits, brain and possibly the spinal cord is necessary in order to confirm or refute areas of demyelination. It should also be stressed that ischaemic optic neuropathy in relatively young patients may be a manifestation of systemic hypertension, embolic disease, connective tissue disorders, systemic arteritides or migraine. Therefore, such conditions should be excluded before a patient's ischaemic optic neuropathy can be attributed to IBD.

In patients suspected of having optic nerve involvement related to IH, brain MRI and cerebrospinal fluid pressure measurement might be necessary diagnostic procedures.

In IBD patients treated with anti-TNF α agents, it is important to discriminate between the demyelinating and the toxic type of optic neuropathy. Based on characteristic symptoms and signs already described, the ophthalmic clinical examination can often distinguish between the two entities, but MRI is valuable in documenting or excluding demyelination of the optic nerve.

3.3. Treatment

Unfortunately, no specific therapy has been found useful for patients with neuroretinitis, papillitis and ischaemic optic neuropathy and the prognosis is highly variable. Regarding patients with optic neuropathy, the recommended treatment typically consists of pulse methylprednisolone 1000 mg/day for three days followed by oral prednisolone 1 mg/kg/day tapered over few weeks. The prognosis for visual recovery is typically very good.

In cases of optic nerve involvement secondary to IH, the reduction of cerebrospinal fluid pressure with oral acetazolamide or, in refractory cases, with a shunt procedure is necessary. The prognosis on the visual function depends on how promptly and efficiently the intracranial pressure is controlled. Because of variations in the duration of IH, the level of the intracranial pressure and the individual patient's optic nerve susceptibility to damage, frequent visual field examination is necessary during the follow-up period so that the effectiveness of therapy is judged.

Similar to idiopathic or MS-related optic neuritis, the usual treatment of optic neuritis related to either IBD or the use of anti-TNF agents consists of pulse methylprednisolone 1000 mg/day for three days followed by oral prednisolone 1 mg/kg/day tapered over few weeks. The prognosis is very good with complete recovery being the rule.⁸⁰ Unfortunately, no specific therapy can be offered for the more rare toxic variety of optic neuropathy described with anti-TNF α agents and the response to steroids is very poor.

4. Conclusions

This review could not identify a sufficient number of methodologically rigorous, high quality studies describing the clinical characteristics and epidemiology of extraintestinal complications involving the optic nerve and the other

structures of the orbit in patients with IBD. This scarceness of information most probably reflects the rarity of these events. However, the possibility that such complications may sometimes remain unrecognized cannot be dismissed. Despite the fact that most of the available information comes from case reports, the existing body of knowledge offers an important, albeit fragmented, insight into the clinical features and the treatment strategies for these complications.

In IBD patients, extraintestinal complications involving the optic nerve and the other structures of the orbit are rare but potentially serious, as they may lead to permanent loss of vision. Close cooperation between ophthalmologists and gastroenterologists is necessary for the successful management of these patients.

4.1. Methods of literature search

The MEDLINE database was used for the literature search of this review. Articles irrespective of the year of publication were used if deemed appropriate. The search included the following keywords and their combinations with appropriate Boolean operators: anti-TNF, Crohn's, demyelinating neuritis, inflammatory bowel disease, optic nerve, optic neuritis, orbit, orbital inflammatory disease, orbital pseudotumor, orbitopathy, retrobulbar neuritis and ulcerative colitis. After retrieving pertinent articles using these keywords, a search was conducted through the literature cited in these articles and additional papers were identified. Papers in languages other than English were also surveyed. Medical Subject Headings (MeSH) searches were also conducted. The latest literature search was performed in August 22nd 2012.

Conflict of interest statement

None of the authors has any conflict of interest to report that may be related to this submission.

Acknowledgment

No funding by any private or public party was received for this work.

Author contributions: AK and AID wrote the manuscript and IA, KHK, MA and EVD reviewed it for intellectual content. The authors would like to thank Dr. Aristeidis Katsanos and Mariana Zikou for preparing the artwork of this review.

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